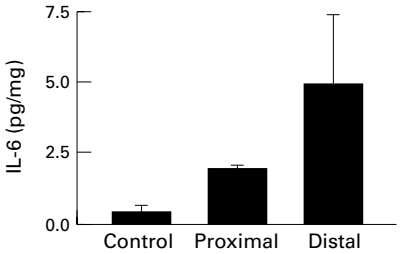
informed consent was obtained for tissue collection, and the study had ethics committee approval. Control dorsal root ganglia were obtained from four subjects and segments of normal nerve from five subjects at postmortem, with a mean delay of 36 hours after death; all died from myocardial causes. Tissue extracts prepared as previously described[3 4] were analysed for IL-6 using an enzyme immunoassay (Pelikine Compact™, Eurogenetics, UK Ltd, Middlesex, UK) with recombinant human IL-6 standard calibrated against the World Health Organisation (WHO) First International Standard 89/548. For immunohistochemistry, frozen sections (8 μm) were fixed in 4% paraformaldehyde in phosphate buffered saline for 30 minutes. Sections were incubated with monoclonal antibodies to IL-6 (CLB.IL-6/7 20 μg/ml, diluted 1:400; gift from K Nordlind, Sweden, or ref No 1618–01, Genzyme, USA) and immunoreactivity to IL-6 visualised using a standard immunoperoxidase method (ABC; Vector Labs, UK) with nickel enhancement as described elsewhere.[3 4] Specific immunoreactivity was extinguished by a concentration of rhIL-6 (ImmunoKontact, Frankfurt, ref 111–40–136) in the range 0.01–0.1 μg/ml. For western blotting, tissue extracts were separated by gel electrophoresis on 15% acrylamide gels and then electrophoretically transferred to nitrocellulose membranes (Hybond Super, Amersham) using a semidry transblotter. Strips were blocked in a solution of 5% non-fat milk in phosphate buffered saline (PBS) containing 0.05% Tween-20 for 1 hour and then probed with CLB.IL-6/7 (with or without IL-6 peptide, 20 μl) at a final titre of 1:1000, for 2 hours. The strips were then incubated with anti-rabbit HRP (Sigma) at 1:10,000 dilution for a further 30 minuttes. Bands were then visualised on *x* ray film after treatment with ECL reagents (Amersham).

Concentrations of IL-6 were increased in injured nerves (figure). The increase was greater in nerve segments distal to injury, but IL-6 concentrations in both proximal and distal segments were both significantly increased compared with controls ($p<0.01$, Mann-Whitney test). Concentrations of IL-6 were greatly raised in two avulsed dorsal root ganglia obtained 3 and 4 days after injury (354 pg/mg and 128 pg/mg). At longer operative delays after injury, IL-6 concentrations in avulsed dorsal root ganglia approached the range of values obtained for postmortem controls (4.9 (SD 2.9) pg/mg for operative delays from 1 week to 15 months, and 0.2 (SD 0.06) pg/mg for controls). Western blotting showed the presence of an expected strong 29 kDa band in detergent extracts of injured nerve, which was abolished in the presence of excess synthetic IL-6. Immunohistochemical studies with both antibodies demonstrated IL-6 staining within the soma of avulsed dorsal root ganglion neurons of all sizes, particularly of small size. Immunostaining of postmortem ganglia seemed similar in pattern, but was generally weaker. Interleukin-6 immunoreactivity was also seen in nerve-like structures within the dorsal root ganglia and distal injured nerve segments.

The pattern of changes of IL-6 in injured nerves and dorsal root ganglia differs from that seen for other neurotrophic factors, such as nerve growth factor (NGF) and glial-derived neurotrophic factor (GDNF).[3 4] Concentrations of IL-6 were usually higher in distal nerve segments when compared with those proximal to the site of injury: this seems



IL-6 immunoreactivity in human nerve tissues. Assay concentrations of IL-6 in extracts of human nerve, comparing segments proximal and distal to injury with control postmortem nerve.

to result from IL-6 synthesis in Schwann cells in Wallerian degeneration, as shown by immunostaining, and previous animal model studies.[2] Interleukin-6 and its receptor have been shown to be required for normal nerve regeneration in animal models, which may be enhanced with exogenous IL-6.[1] The injured nerves presumably take up IL-6 synthesised in the Schwann cells, and transport it proximally, which accounts for the higher IL-6 concentrations in proximal segments of injured nerves in comparison with controls. Anterogradely transported IL-6, if released in the spinal cord, may play a part in pain processing, for which there is some evidence from animal models. In this study, the most remarkable finding was the very high concentration of IL-6 in extracts of the acutely avulsed dorsal root ganglia, with much smaller increases at later times after injury. The acute increase of IL-6 could originate from sensory cell bodies themselves, as has been shown with IL-6 mRNA in situ hybridisation studies in rat sensory ganglia after peripheral nerve injury,[5] or from inflammatory cells. This increase may have autocrine/paracrine effects, which may aid cell survival, or have a role in sensory or sympathetic sprouting.

We conclude that IL-6 is a significant factor in the events after nerve injury in humans, particularly in sensory neurons. The potential therapeutic role in nerve repair for recombinant human IL-6, and agents that modulate its action, deserves further investigation.

G SALDANHA
K J BÄR
Y YIANGOU
P ANAND
Division of Neuroscience and Psychological Medicine, Imperial College of School of Medicine, Area A, Ground Floor, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

R BIRCH
T CARLSTEDT
Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, Stanmore, Middlesex, UK

J M BURRIN
St Bartholomews and The Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, Royal London Hospital, London, UK

Correspondence to: Professor P Anand

1 Hirota H, Kiyama H, Kishimoto T, *et al*. Accelerated nerve regeneration in mice by upregulated expression of interleukin-6 and IL-6 receptor after trauma. *J Exp Med* 1996; **183**:2627–34.
2 Bolin LM, Verity AN, Silver JE, *et al*. Interleukin-6 production by Schwann cells and induction in sciatic nerve injury. *J Neurochem* 1995;**64**:850–8.
3 Bar KJ, Saldanha GJ, Kennedy AJ, *et al*. GDNF and its receptor component Ret in injured human nerves and dorsal root ganglia. *Neuroreport* 1998;**9**:43–7.
4 Anand P, Terenghi G, Birch R. *et al*. Endogenous NGF and CNTF levels in human peripheral nerve injury. *Neuroreport* 1997;**8**: 1935–8.
5 Murphy PG, Grondin J, Altares M, *et al*. Induction of interleukin-6 in axotomized sensory neurons. *J Neurosci* 1995;**15**:5130–8.

Crossed face apraxia

Apraxia refers to the disorder of movement planning and execution that cannot be accounted for by motor or sensory deficits nor by other cognitive impairments. The term apraxia encompasses several different deficits, including "face apraxia", which defines the impairment of movements performed within the district of the cranial nerves. Group studies have shown that face apraxia results from lesions of the left hemisphere.[1] However, a few cases can be gleaned from the literature of patients whose face apraxia followed lesions in their right hemisphere and was mentioned in fleeting comments.[2–4]

Face apraxia has generally been equated to oral apraxia and tests aimed at assessing it only comprise items exploring skilled movements of the lips, cheeks, and tongue. However, several early authors reported on patients with face apraxia also showing movement deficits of the eyes and eyebrows.[5] Some anecdotal evidence of upper face apraxia is also reported in more recent investigations.[6] We report on a patient, who, 2 years after a right hemispheric lesion, showed severe face apraxia for movements of both the lower and the upper parts of the face. A 55 year old artist with 17 years of education had an ischaemic stroke in August 1997. A series of CT and MR scans showed a right frontoparietal insular hypodensity also encroaching on the anterior region of the right internal capsule and of the right deep nuclei, sparing the mesial and the anterior part of the parietal lobe. He had always been right handed, scored 100% right handed on both the Edinburgh handedness questionnaire[7] and the 12 question handedness inventory.[8] He also denied familiarity for left handedness. We examined the patient in October 1999, 5 months after the end of his rehabilitation therapy and more than 2 years after his stroke. He still showed a severe left paresis, hemianopia, and a deficit of the lower facial nerve. No further deficits of the cranial nerves were seen. In particular, spontaneous movements of the oculomotor nerves were normal. The patient did not show general cognitive impairment: his scores on intelligence tests were well within the normal range. At the time of our assessment he did not show clear evidence of visuospatial neglect which was mentioned in the clinical notes at onset. He performed flawlessly tasks assessing the ability to search for particular targets, in reading, or in line bisecting, although he omitted a few left details in copying complex geometrical drawings. During neurological examination the patient proved unable to close his eyes on verbal command. He failed even when the examiner showed him how to do it. He was therefore submitted to a battery of tests assessing apraxia including the upper and lower face apraxia test.[9] The nine upper and 29 lower items of the test were performed first on imitation and then, considering the possibility that the patient could have some difficulty in perception, on verbal command. On imitation, the patient scored 2/45 and 320.25/435 (adjusted scores) on the upper and lower face

sections of the test respectively, both well below the inner tolerance limit cut off scores (38.43/45; 400.04/435). On command he failed all items of the upper face test and he failed the same items of the lower face test which he failed on imitation.

His errors were perseveration of the previous item or substitutions with another movement—for instance, when asked to make a clip-clop noise with his tongue, he showed his teeth, then made his teeth chatter. Similarly, asked to close his eyes, he said "yes" at first, then he opened his mouth, then he tried to show his tongue. He was unable to close either his right or his left eye, to look leftward or rightward keeping his head motionless, or to wrinkle his forehead or his nose.

The patient's face apraxia could not be due to motor impersistence because he was not required to hold a position for a given time.[10] Moreover, the fact that his face apraxia was long lasting excludes the possibility that upper face apraxia has to be drawn back to diaschisis or other similar phenomena. Finally, neglect had recovered at the time of testing and there was no cognitive deterioration to account for the presence of this symptom.

Ideomotor apraxia was also assessed by means of a 24 item test.[11] His score with the right arm and hand was normal (64/72, cut off score=53). The patient was not aphasic; his language was emitted with a normal prosody, was well articulated, informative, and without qualitatively aphasic errors.

This case points to a possible role that the right hemisphere might have in normal facial praxis, both for the lower and upper face areas, in some people. Moreover, it confirms the dissociation between face apraxia and aphasia, as well as between limb and face apraxia.

C PAPAGNO
Dipartimento di Psicologia, Università di Palermo, Italy

S DELLA SALA
Department of Psychology, King's College, University of Aberdeen, AB24 2UB Aberdeen, UK

Correspondence to: Professor S Della Sala
sergio@abdn.ac.uk

1 De Renzi E. Apraxia. In: Denes F, Pizzamiglio L, eds. *Handbook of clinical and experimental neuropsychology*. Hove: Psychology Press, 1999:421–41.
2 Kleist K. *Gehirnpathologie. Vornehmlich auf Grund der Kriegserfahrungen.* (Brain pathology based on war experience). Leipzig: Johan Ambrosius Barth, 1934.
3 Kramer JH, Delis DC, Nakada T. Buccofacial apraxia without aphasia due to a right parietal lesion. *Ann Neurol* 1985;**18**:512–14.
4 Marchetti C, Della Sala S. On crossed apraxia. Description of a right-handed apraxic patient with right supplementary motor area damage. *Cortex* 1997;**33**:341–54.
5 Lewandowsky M. Über apraxie des Lidschlusses. (About lid apraxia). *Berliner Klinische Wochenschrift* 1907;**29**:921–3.
6 Lebrun Y. Apraxie de la parole et apraxia bucco-faciale (Speech apraxia and oral apraxia). In: Le Gall D, Aubin G, eds. *L'apraxie*. Marseille: Solal, 1994:160–82.
7 Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 1971;**9**:97–113.
8 Annett MT. The binomial distribution of right, mixed and left handedness. *Q J Exp Psychol A* 1967;**19**:327–333.
9 Della Sala S, Spinnler H, Venneri A. Un test di aprassia della faccia: dati normativi e validazione su cerebrolesi sinistri e dementi di Alzheimer (A test of face apraxia: norms and validation with a sample of focal brain damaged patients and a sample of patients with Alzheimer's disease). *Archivio di Psicologia Neurologia e Psichiatria* 2000 1998;**49**:346–57.
10 De Renzi E, Gentilini M, Bezzolli C. Eyelid movement disorders and motor impersistence in acute hemisphere disease. *Neurology* 1986; **36**:414–18.
11 De Renzi E, Motti F, Nichelli P. Imitating gestures: a quantitative approach to ideomotor apraxia. *Arch Neurol* 1980;**37**:6–10.

A case of Bickerstaff's brainstem encephalitis mimicking tetanus

Bickerstaff's brainstem encephalitis is characterised by acute ophthalmoplegia and ataxia with progressive consciousness disturbance.[1] Although Bickerstaff described rigidity in the recovery phase,[1] rigidity in the clinical course of Bickerstaff's brainstem encephalitis has rarely been reported.[2] We encountered a case in which the initial diagnosis was tetanus, because of the progression of severe rigidity and risus sardonicus, but which turned out to be Bickerstaff's brainstem encephalitis owing to the presence of anti-GQ1b IgG antibody.

A 23 year old man who had had no prior apparent infectious episode began to show dysaesthesia, clumsiness, and slight weakness of all limbs (day 1). Due to rapid exacerbation of these symptoms he was admitted to a hospital the next day. On day 3, he became irritable because of increased anxiety, although he was alert and completely oriented. He was transferred to another hospital for further treatment. There he required assistance in walking because of new severe rigidity in all his limbs. Oral haloperidol (maximum dose 20 mg/day) was given for 10 days to reduce his anxiety, but his symptoms did not lessen. Treatment with intravenous methylprednisolone (1000 mg/day) from day 14 to 16, as well as acyclovir (1500 mg/day) given intravenously, failed to ameliorate his symptoms. On day 17, he was transferred to our hospital for further evaluation and treatment.

Physical examination on day 17 showed a body temperature of 37.0°C, blood pressure 130/80 mm Hg, pulse rate 100 beats/min, respiratory rate 12 /min, and severe hyperhidrosis. Neurological examination showed that he was alert and well oriented. The pupils were isocoric and round but mydriatic. Light reflexes were prompt. Bilateral blephaloptosis was present. Extraocular movement was completely inhibited vertically and horizontally. Restriction of mouth opening and dysarthria similar to risus sardonicus were caused by increased tonus of the masseter muscles. Neither tongue atrophy nor fasciculation was present. Tests for muscle strength and coordination could not be made due to severe rigidity of the neck, trunk, and limbs. Deep tendon reflexes were absent, probably secondary to the rigidity. The Babinski response was negative bilaterally. Voluntary movements were markedly slow, and sitting balance was poor. Opisthotonus was not present. No abnormality was found in the sensory examination. Because of Forley catheter placement due to the patient's severe general condition, we did not evaluate his bladder function.

White blood cell count was 13 320 /mm^3 (84% neutrophils), but the erythrocyte sedimentation rate and C reactive protein concentration were normal. Protein in CSF was 144 mg/dl with normal cellularity. No oligoclonal IgG bands were detected in the CSF. Magnetic resonance imaging detected no abnormalities in the brain stem. An EEG was normal. Motor nerve conduction velocities and compound muscle action potentials measured in the right median, ulnar, and posterior tibialis nerves were normal, but no F waves were evoked. Antidromic sensory nerve velocity in the right median nerve was normal, but no sensory activation potentials were evoked in the right ulnar and posterior tibial nerves.

Based on his clinical course and the physical examination, the tentative diagnosis was general tetanus. On day 18, intravenous piperacillin sodium (4000 mg/day) and oral dantrolene sodium (25–50 mg/day) were started. On day 19, 4500 IU human anti-tetanus immunoglobulin (Tetanobulin®, Yoshitomi, Tokyo, Japan) was infused. On day 20, his bilateral blephaloptosis and rigidity of the limbs began to lessen. Subsequently his symptoms and signs improved dramatically. On day 24 he could turn himself over in bed. On day 25 ophthalmoplegia was ameliorated with slight limitation of lateral gaze. On day 26 he could sit independently. On day 32 he could stand without assistance, and on day 37 he could walk independently. During the recovery phase, no ataxia was seen. He has not had a relapse for 2 years and 6 months.

After his recovery, we evaluated the antiganglioside antibodies and antitetanus antibody activity in his serum. An enzyme linked immunosorbent assay[3] showed that serum IgG on day 19 had high (4000) anti-GQ1b antibody titre. The IgG antibodies did not react with GM1, GM2, GD1a, GalNAc-GD1a, GD1b, or GT1b. Thin layer chromatography with immunostaining confirmed that the patient's IgG bound strongly to GQ1b, but not to GM1, GD1a, GD1b, or GT1b. No anti-GQ1b IgG antibody was detectable (titre<500) 2 years and 6 months after the onset of neurological symptoms. By contrast, the neutralising antitetanus antibody activity in the serum on day 17 was 0.41–0.75 IU/ml, sufficient for protection against tetanus infection.[4]

Serum anti-GQ1b IgG antibodies have been found in patients with Miller Fisher syndrome, Guillain-Barré syndrome with ophthalmoparesis, acute ophthalmoparesis, and Bickerstaff's brainstem encephalitis.[5] Albumino-cytological dissociation in CSF and poor F wave response of the examined nerve are compatible with Miller Fisher or Guillain-Barré syndrome. The clinical findings, most characteristic of this patient, however, were severe rigidity of the face, neck, trunk, and limbs, which has not been described in Miller Fisher syndrome, Guillain-Barré syndrome, or acute ophthalmoparesis. The extrapyramidal side effect of haloperidol was unlikely because rigidity was present before the drug was administered. Bickerstaff reported the development of parkinsonism, including rigidity, within 2–4 weeks of onset and during the recovery phase in Bickerstaff's brainstem encephalitis, with the exception of a fatal case in which parkinsonism developed before maximal disability.[1] Our patient showed rigidity from the beginning. Although an overlap of Guillain-Barré syndrome could not be excluded,[2] our diagnosis was Bickerstaff's brainstem encephalitis, because the patient's case was close to the exceptional one reported by Bickerstaff. Antitetanus imunoglobulin is comprised of high dose polyclonal IgGs to tetanus toxin and other types of IgGs and IgMs, and it may have had an effect similar to that of intravenous immunoglobulin in our patient. His dramatic recovery immediately after antitetanus immunoglobulin administration could not be explained as part of a natural course. Although the mechanism for the early appearance of rigidity in our